Hematopoietic Stem Cell Engraftment of Rare Niches Corrects Severe Lymphoid Deficiencies in the Absence of Myeloablation

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Hematopoietic stem cells (HSC) occupy unique niches within an organism and are thought to prevent productive engraftment of transplanted donor HSC by filling all of the available niches[1]. By transplanting congenically marked CD45.1 HSC into tolerant CD45.1 x CD45.2 recipients, we demonstrate that approximately 0.1% of all HSC niches are available for productive engraftment in wild type non-myeloablated hosts. Productive engraftment of unconditioned CD45.2 recipients, however, is never seen. Strikingly, transplantation of purified wild type HSC into non-irradiated recombination activating gene 2 and interleukin-2 receptor common gamma chain-deficient mice ($RAG2^{-/-}\gamma c^{-/-}$), which lack mature B, T, or natural killer cells[2], leads to a rapid and dramatic correction of lymphoid deficiencies and persistent myeloid contribution despite few available HSC niches. The lymphoid correction occurs largely due to an opportunistic expansion of donor-derived cells at the pro-B cell and DN1 thymocyte stages. After HSC-mediated correction of lymphoid deficiencies, we show that these mice can respond normally to antigenic challenge. Using a panel of additional genetic mutants, we demonstrate that access to these rare HSC niches is regulated primarily by host CD4+ T cells that can recognize subtle minor histocompatibility differences. Finally, we show that aged mice, which have reduced lymphoid function relative to younger animals, reject HSC transplants more slowly than do young animals. Our data allow for the quantification of open HSC niches in a non-myeloablative setting and show that small numbers of productively engrafted wild-type HSC within these rare niches can rescue severe hematopoietic deficiencies. Our experiments emphasize that HSC-mediated correction of lymphoid deficiencies is by no means limited by HSC niche space in non-myeloablated animals

Our data show that available HSC niches exist in normal unconditioned animals and that these rare niches can be engrafted by transplanted HSC to correct severe lymphoid deficiencies in the absence of mobilization or cytotoxic stimuli. Thus, the major barrier to HSC-mediated correction of lymphoid deficiencies is CD4+ T cell-mediated rejection rather than a lack of HSC niche space.

References:

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